Clinics in Dermatology (xxxx) **xx**, xxx

ELSEVIER

Clinics in Dermatology

Cutaneous leishmaniasis: A great imitator

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Abstract Cutaneous leishmaniasis (CL) is called "the great imitator," because it can mimic almost all types of dermatoses. This similarity may sometimes lead to misdiagnosis, resulting in inappropriate treatment and morbidities. Atypical forms occur due to the interaction between parasitic factors and the host immune response. Secondary infection or mistreatment of CL can also alter the natural course, resulting in bizarre and misdiagnosed cases. Atypical leishmaniasis should be considered in longstanding and painless lesions that may simulate erysipelas, dermatitis, verruca, herpes zoster, paronychia, and sporotrichosis. Less commonly, sarcoidosis, deep mycosis, basal and squamous cell carcinoma, cutaneous lymphoma, or pseudolymphomalike lesions may need to be considered in the differential diagnosis. A high index of suspicion is required to consider a diagnosis of CL, especially in nonendemic or newly endemic regions. Smear, histopathologic examination, culture, and polymerase chain reaction serve as important tools to differentiate CL from its clinical and histologic look-alikes. CL is discussed from various perspectives, with emphasis on CL and its broad differential diagnosis.

Introduction

Leishmaniasis, caused by over 20 species of the genus *Leishmania*, is a neglected vector-borne parasitic infection that gives rise to a broad spectrum of diseases with protean manifestations.[1,2] It is related to a variety of risk factors, such as poverty, malnutrition, migration, and poor housing conditions. Its incidence is on the rise in certain geographic areas of the world, including Syria, Turkey, and Jordan, due to war-associated migration and the resulting refugee crisis.[3–8] Increased global travel also contributes to the growing problem of imported leishmaniasis.[9–12] The most common form of leishmaniasis is cutaneous leishmaniasis (CL), which is estimated to affect 600,000 to 1 million new cases worldwide annually.[13] Although not life-threatening, CL is an important entity to recognize and treat, because it can be associated with permanent scar formation, decreased quality of life, stigmatization, and long-term psychologic consequences.[4,14–16] Prevention and control requires a multifaceted approach including, but not limited to, vector control, disease surveillance, timely diagnosis, and appropriate treatment.[13]

Historical perspective

Leishmaniasis has been documented throughout history.[17,18] A molecular paleopathologic study demonstrated evidence of mitochondrial DNA of *L. donovani* in Egyptian mummies,

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https://doi.org/10.1016/j.clindermatol.2019.10.008
0738-081X/

suggesting that visceral leishmaniasis can be traced to ancient Egypt.[18,19] The Oriental sore is believed to have been first described by Avicenna (980-1037) as *Balkh sore*.[18,20,21] It has since been known by several names, such as *Aleppo boil* and *Baghdad boil*.[17,18,20] The active inoculation of virulent *Leishmania* organisms from an infected exudate to develop immunity, known as *leishmanization*, had been practiced for centuries before it was abandoned mainly due to the risk of development of large, persistent lesions.[22–24]

The causative organism of leishmaniasis was named after the Scottish pathologist William Boog Leishman (1865-1926), who discovered ovoid bodies in postmortem smears from the spleen of a soldier who had died of kala-azar while he was stationed in India. He coined the term *dum-dum fever*, which he interpreted as a form of trypanosomiasis.[17,18,25–27] Later in the same year, Charles Donovan (1863-1951) reported that he had detected similar bodies in splenic samples of patients thought to have died of chronic malaria.[28] Having examined Donovan's preparations, the British physician Ronald Ross (1857-1932) concluded that the ovoid bodies described by Leishman and Donovan represented a novel protozoan microorganism, for which he proposed the name *Leishmania donovani* in a follow-up publication.[29,30]

Microbiologic perspective

The main transmission of *Leishmania* species is anthroponotic or zoonotic, via phlebotomine sandflies, although human-to-human transmission by infected needles, transfusion, or congenital transmission have also been reported.[31–36] The major sources of transmission are usually canines, rodents, or humans, depending on the species of parasite, the genus of vector, and geographic region.[37] Approximately 90 different sandfly species belonging to *Lutzomyia* and *Phlebotomus* genera are found to be vectors that are prevalent in the New World and the Old World, respectively.[31,32,38] More than 20 species of *Leishmania* parasites cause disease in humans, each of which is transmitted by particular species of phlebotomine sandflies that are mostly active from dusk to dawn.[39]

Leishmania species have a dimorphic life cycle beginning at the time the female sandfly feeds on the vertebrate host, letting the promastigote (10-20 μm) inoculate into the mammalian host's skin. The macrophages located in the dermis phagocytize the promastigotes which then transform into intracellular nonflagellated amastigotes (3-5 μm). Inside phagolysosomes, amastigotes multiply by simple binary division until they rupture the cell and infect other mononuclear phagocytes by migrating through regional lymphatics and vascular system.[31,37] During this period, the characteristics of the parasite and the host determine the symptomatology and extent of leishmaniasis, like visceral or cutaneous disease.[39]

Despite being morphologically indiscriminant, *Leishmania* species can be differentiated into their taxonomic profiles by isoenzyme electrophoresis or DNA-based analysis. Isoenzyme analysis is a complicated method which necessitates specific laboratory techniques. DNA-based analysis by polymerase chain reaction (PCR) is not only the most sensitive diagnostic method, but also a valuable tool for species-based identification of the parasite. A reliable classification of the microorganism was shown to help the clinician predict the source of the disease and its prognosis.[37,39,40]

In the Old World type, the most frequent causative species of CL are *L. major*, *L. tropica*, and *L. aethiopica.* Occasionally, *L. donovani* and *L. infantum* or *L. chagasi* can be isolated from simple CL lesions. New World CL that is endemic in Latin America is most frequently due to *L. braziliensis*, *L. mexicana*, and *L. panamensis* or *L. guyanensis.* Occasionally, *L. infantum* or *L. chagasi* can cause simple nodular CL in Central America.[37]

Epidemiologic perspective

As of early 2019, leishmaniasis belonged to the list of 20 neglected tropical diseases according to the World Health Organization.[41] Children suffer from the highest burden of leishmaniasis.[42] *Leishmania* infections are seen in humans in nearly 90 countries located on every continent other than Australia and Antarctica. The parasite can adapt to a variety of ecologic conditions from rain forests to deserts. The disease is widely distributed among the tropical and temperate regions most of which are located in the developing areas of the world.[31,37,39] It is difficult to estimate the exact number of cases due to the changes over time; however, the range of the estimated yearly incidence of CL is between 600,000 and 1 million.[13,39] Changing environmental conditions and human factors like migration or travel habits, increased number of immunosuppressed individuals, or decreased usage of insecticides have an effect on expanding the range of vectors and leishmaniasis; however, in 2015, more than two-thirds of new diagnoses of CL were confined to six countries, namely Afghanistan, Algeria, Brazil, Colombia, the Syrian Arab Republic, and the Islamic Republic of Iran.[13,39] The recent CL epidemic in the Syrian Arab Republic, which has led to outbreaks in Lebanon, Jordan, and Turkey, once more illustrates the association between conflict and leishmaniasis, like the previous outbreaks in Iran, Iraq, and Colombia.[7,8,43–45] Outbreaks may also occur with the effect of human invasion of forest areas that are inhabited by sandflies or exposure of susceptible hosts in endemic areas.[37]

In the United States, south-central Texas is such an area endemic for CL.[46,47] According to a more recent study, endemic human leishmaniasis is diagnosed more frequently than travel-acquired disease in Texas, and it appears likely that leishmaniasis may be underreported.[48,49]

Clinical perspective

Three main clinical forms of leishmaniasis have been defined.[13,50] The clinical presentation is dictated by the interplay of parameters related to the parasite (eg, species, virulence, and tropism) and the host immune response.[4,5]

Cutaneous leishmaniasis

Based on the geographic region, CL is generally subdivided into two categories, Old World and New World, both of which typically begin as a small papule at the site of inoculation, usually at an exposed body site such as the head or extremities. This papule slowly enlarges to evolve to a nodule that progressively ulcerates. The ultimate ulcer is characteristic of CL and self-heals over 3 to 18 months, depending on the specific species. Up to 10% of CL cases are estimated to show progression, become chronic, and exhibit more severe clinical features.[4,5,51,52]

There are two major forms of Old World CL, namely zoonotic (also known as early ulcerative, usually caused by *L. major*) and anthroponotic (also known as late ulcerative, caused by *L. tropica*).[53,54] Anthroponotic CL is transmitted from human to human via vector, seen mainly in urban areas, and characterized by a more chronic course.[55]

The two rare, albeit important, manifestations of Old World CL are leishmaniasis recidivans (LR) or chronic lupoid leishmaniasis. LR refers to the appearance of new papular lesions during or after the healing of the acute lesion. Clinically, it commonly occurs as fine, scaly, erythematous papules in the periphery of healed lesions of CL. The peripheral papules may exhibit an apple-jelly color on diascopy, the same as lupus vulgaris, but are not destructive (Figure 1). LR lesions may persist individually or coalesce, and slowly enlarge for many years.[5,55–57]

In a small proportion of patients with CL, the initial lesions of CL do not improve in the expected period and persist. If the infection lasts more than 2 years, it is considered chronic CL (Figure 2). Lesions of chronic CL may persist for several years, and the parasite burden is low. Usually, they do not ulcerate and are resistant to treatment.[50,56,58] Chronic lupoid leishmaniasis bears clinical and histopathologic resemblance to the lupus vulgaris form of cutaneous tuberculosis, posing a diagnostic challenge.[59,60]

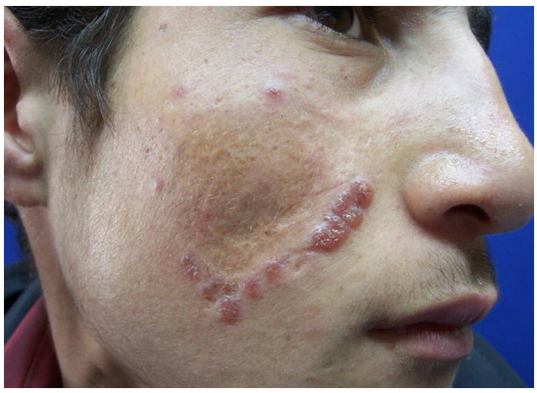

Fig. 1 Leishmaniasis recidivans; atrophic healed center and new-onset papules in the periphery.

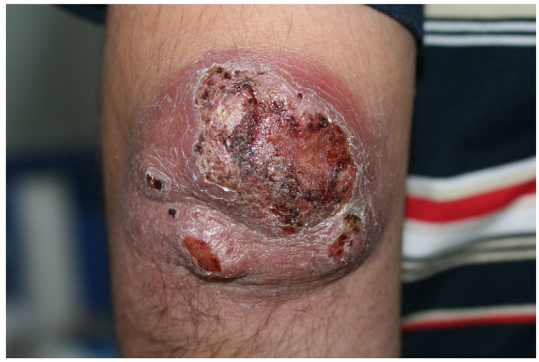

Fig. 2 Chronic cutaneous leishmaniasis; tumoral lesion on the right elbow for 4 years. Histopathologically, it had been diagnosed as lupus vulgaris and was unresponsive to antituberculous drugs for 9 months.

Diffuse CL and disseminated CL are typically linked to immunosuppression and deserve special mention. Diffuse CL clinically resembles lepromatous leprosy and manifests with multiple nonulcerating papules and papulonodules located on the face and extremities. It is usually associated with a reduced cellular immune response.[4,46] Disseminated CL, is characterized by numerous lesions similar to those of classic CL, usually accompanied by ulceration or mucosal involvement. This form is seen in Latin America and associated with the presence of anti-*Leishmania* antibodies and decreased production of interferon-gamma and tumor necrosis factor-alfa.[4,61] Diffuse CL and disseminated CL exemplify how the different cellular immune responses translate into distinct clinical manifestations.

Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis is characterized by destruction of the lips, palate, and nasal septum, potentially leading to perforation of the nasal septum or larynx.[13,62] The majority of cases are seen in Bolivia, Brazil, Ethiopia, and Peru and caused by *Leishmania* species in the *Viannia* subgenus (also known as the *L. braziliensis* complex).[13] Mucocutaneous leishmaniasis can be permanently disfiguring and disabling, causing extensive loss of tissue of the oropharynx, nose, and lips and has the potential to be life-threatening.[11,62,63]

Visceral leishmaniasis

Newly acquired infection, mainly with *L. infantum* or *L. chagasi* among the pediatric population and *L. donovani* in adults, can be clinically expressed on a wide spectrum ranging from subclinical to systemic infection with full-blown

manifestations.[64] The latter results from systemic dissemination of the parasite to the bone marrow and internal organs.[46] The onset can be abrupt or slow, with the incubation period ranging from 2 weeks to 36 months.[4,46] The most common systemic findings are anorexia, wasting, cough, pallor, night sweats, organomegaly, lymphadenopathy, and fever, which may be intermittent or continuous.[46] Untreated visceral leishmaniasis is fatal in over 95% of cases, usually within 2 years due to sepsis, multisystem disease, or severe anemia.[4,13] An infrequent, albeit well-known finding that led to the name *kala-azar* (which means black fever in Hindi), is cutaneous hyperpigmentation, which is thought to result from hormonal alterations.[4,53,64,65] Other cutaneous manifestations of visceral leishmaniasis can be divided into disease-specific lesions at infected areas (eg, papules, nodules, or ulcers) and nonspecific lesions (eg, purpura, kwashiorkorlike hair discoloration, and xerosis).[46]

Visceral leishmaniasis and HIV coinfection deserves further mention in that this combination poses diagnostic and therapeutic complexities and challenges.[66,67] From a microbiologic standpoint, HIV and *Leishmania* share a common immunopathologic mechanism that involves dendritic cells and macrophages. The two microorganisms appear to have a bidirectional relationship in that HIV infection dramatically increases the risk of developing visceral leishmaniasis, and similarly, *Leishmania* infection of monocytes is thought to promote HIV replication.[1,4,46] HIV and visceral leishmaniasis coinfection often leads to reduced therapeutic response, and higher rates of drug toxicity, relapse, and mortality.[68]

Post–kala-azar dermal leishmaniasis (PKDL) is considered an immunologically mediated sequela of visceral leishmaniasis primarily seen in the Sudan and India.[13,46] Onset is usually 6 months to 1 or more years after treatment, but it can occur up to 20 years later.[13,46] Although differences exist in the description of cutaneous findings based on geographic location and presence or degree of immune suppression, the hallmark lesions of PKDL can be broadly summarized as erythematous or hypopigmented macules, papules, skin-colored nodules, and malar erythema.[46,69–73] Typically, lesions first appear in the perioral region and subsequently become generalized.[70,71] Preservation of sensation in lesional skin helps to distinguish PKDL from leprosy.[4]

Table 1 Clinical clues for the diagnosis of CL

- Travel history to or residence in regions where leishmaniasis is endemic
- Usually small number of lesions (one to three)
- Painless lesions
- Localization on uncovered body areas
- Patients report history of several months or slow change over weeks
- No response to previous systemic or topical antibiotic treatments
- Rubbery consistency on palpation

Diagnosis

Diagnosis of CL can be made by clinical, parasitologic, or immunologic approaches (Table 1). A high index of suspicion is required to consider CL clinically, especially in nonendemic or newly endemic areas.[5,47] Sandfly bites may be painless and go unnoticed by the patient, which makes anamnesis less reliable for clinical diagnosis.[59] In some settings, a clinical diagnosis based on typical lesion morphology in a patient with relevant history has a significant pretest predictive probability; nevertheless, a definitive parasitologic diagnosis is preferable for accurate diagnosis, appropriate drug selection, and prognostic prediction.[31,37] Because no gold-standard parasitologic diagnostic test is currently available, it is recommended to combine histopathology, culture, and DNA amplification techniques to increase sensitivity and provide identification on a species basis. Because almost all of the specimen collection techniques and laboratory diagnostic procedures of *Leishmania* require highly specific knowledge, it is recommended to contact a reference laboratory in advance to obtain specimens. Additionally, simultaneous diagnostic approach for other possible etiologies (eg, sporotrichosis, blastomycosis, mycobacterial infections, syphilis) should be considered.[74]

Dermatoscopy

Various dermatoscopic features, such as white starburst-like pattern, teardroplike structures, yellow tears, and salmon-colored ovoid structures, have been described, although the specificity of these findings may require further investigation.[75–79]

Leishmania smear

In the initial evaluation, it is recommended to obtain a smear sample, to be followed by direct examination with Giemsa stain. A smear is considered an inexpensive, simple, and rapid approach for the diagnosis of CL. Four different methods can be employed to obtain samples: slit-skin, scraping, touch (imprint) smear, and fine-needle aspiration.[5] Although detection of *Leishmania* amastigotes in the microscopic evaluation is sufficient for diagnosis, it requires substantial expertise.[74] More recently, a diagnostic algorithm has been proposed where a positive direct microscopic examination using smear is followed by anti-*Leishmania* treatment, whereas a negative initial examination should be further worked up with a skin biopsy.[5]

Culture

Culture of the parasite should be attempted, because isolation of the parasite in culture media permits confirmation of the diagnosis, and the isolates may be used for further testing purposes. The specimen obtained for culture can also be

evaluated for other possible agents. Sampling for parasitologic culture requires a sterile technique with avoidance of residual iodine and alcohol that could affect parasite growth on culture media.[74] Because it is a highly fastidious microorganism, transport in an appropriate medium is one of the most crucial steps in the culturing process of *Leishmania.* The reference laboratory should be contacted before collection of the samples to obtain transport and culture media. If this is not feasible, specific recommendations from the Centers for Disease Control and Prevention may be used.[40,74] Novy-MacNeal-Nicolle (NNN) is a special culture medium used to grow *Leishmania* microorganisms.[46,80] The sensitivity of the combination of direct parasitic evaluation and the culture methods ranges from 50% to 90% depending on the lesion and parasite characteristics.[37] The growth of promastigotes on culture media takes 2 days to 2 weeks. A sensitive microcapillary culture method has been developed to provide a rapid diagnosis of CL. Compared with the traditional culture method, the microcapillary culture method reportedly had a higher sensitivity, faster detection time, and required a smaller inoculum size of parasites.[81] Reference laboratories perform isoenzyme analysis or DNA-based analysis to identify the species after isolation in the culture.[74] There is some evidence that identification of the specific species may assist with therapeutic decision-making, particularly in New World CL.[4,5,74]

Polymerase chain reaction

PCR analysis is currently the most sensitive method for detection of *Leishmania.* Almost any tissue specimen that is handled appropriately after collection can be used for PCR. The method also permits species-based identification of the parasite.[74] The sensitivity of diagnostic methods generally decreases as lesions age and the number of parasites decreases[5,57,59,81,82]; however, PCR has a high sensitivity (97% to 100%) regardless of age of the lesion.[82]

Histopathology

Histopathologic examination is an important diagnostic tool that can help with differentiation between conditions mimicking CL. Ideally, a biopsy should be taken of the border of an ulcer or nodule, including affected and unaffected tissue.[59] In all variants of leishmaniasis, histopathologic features depend on the age of the lesion and host-parasite interaction.

Acute lesions of Old World CL and New World CL demonstrate histologic similarities. Early stages of CL are characterized by a dense and diffuse dermal infiltrate of parasitized histiocytes, lymphocytes, plasma cells, and variable numbers of neutrophils. Amastigotes can be identified in 50% to 70% of skin biopsies of Old World CL in early lesions.[59,80] As ulcers become more chronic, they have fewer amastigotes.[59] There may be an uninvolved papillary dermis (Grenz zone).[59,83] With progression of the lesions, epithelioid cell granulomas with giant cells develop in the upper portion of the dermis; with chronicity, small tuberculoid granulomas begin to replace the decreasing number of parasitized histiocytes.[46] Late stages of CL may be accompanied by a large number of plasma cells. Epidermal alterations, such as atrophy, acanthosis, ulceration, or pseudoepitheliomatous hyperplasia, may be seen.[59,83,84] The cicatricial stage is characterized by flattened and hyperpigmented epidermis accompanied by dermal fibrosis.[46] LR lesions have few amastigotes, whereas diffuse CL is characterized by a diffuse infiltrate of macrophages containing amastigotes in the dermis.[59,83]

Leishmania amastigotes, also known as Leishman-Donovan bodies, are found in clusters in the cytoplasm of macrophages, especially in the papillary dermis.[46,59] Extracellular amastigotes are seen infrequently.[53] Each amastigote is a round or oval body measuring 2 to 4 μm in diameter.[83] In addition to routine hematoxylin and eosin staining, Giemsa, Wright, or Feulgen stains can be used to detect the microorganisms.[46,85]

Other diagnostic techniques

Serologic testing can be helpful for the diagnosis of visceral leishmaniasis, however, the available serologic assays are not sensitive or specific enough to be used for CL[37,74] The Leishmanin skin test (Montenegro test or Leishman reaction) is a delayed hypersensitivity test, which is positive in up to 90% of patients with CL or mucocutaneous leishmaniasis of over 3 months' duration.[46,53] Its positivity indicates contact with *Leishmania* but cannot be solely used for diagnosis. The lack of worldwide availability, standardization, or approval reduces the diagnostic utility of Leishmanin skin test.[74] There is an interferon-gamma release assay test that has been developed for epidemiologic purposes, but it is not commercially available.[86]

Differential diagnosis

Cutaneous leishmaniasis has aptly been called one of the "great imitators" in dermatology because of its protean manifestations.[5,87] Most CL lesions are typical and readily diagnosed, whereas diagnosis of unusual clinical presentations can be challenging and delayed, especially in regions where leishmaniasis is not endemic. In such cases, diagnosis can be confirmed by histopathology or parasitologic methods. Lesions may exhibit unusual localization and unexpected numbers, or clinical manifestations may appear with atypical and unusual morphologies.[56,88]

Atypical lesions can show diverse clinical manifestations, such as erysipeloid, sporotrichoid, eczematous, lupoid, verrucous, paronychial, fissure leishmaniasis, chancriform, acneiform, annular, palmoplantar, psoriasiform, and panniculitic forms.[51,88–98] Nodular or nodulo-ulcerative lesions

Table 2 Differential diagnosis of cutaneous leishmaniasis[50,57,59,87,94,96]

Acute cutaneous leishmaniasis:
Impetigo, ecthyma, furunculosis, carbunclosis
- Leprosy
- Tuberculosis cutis verrucosa
- Atypical mycobacterial infections
- Syphilis
- Kerion
- Deep fungal infections (eg, sporotrichosis, blastomycosis, mycetoma, histoplasmosis)
- Sporotrichosis
- Amebiasis
- Molluscum contagiosum
- Verruca vulgaris
- Orf
- Granulomatous rosacea
- Sarcoidosis
- Foreign body granuloma
- Pyogenic granuloma
- Lymphocytoma cutis
- Cutaneous T-cell lymphoma
- Basal cell carcinoma
- Squamous cell carcinoma
- Keratoacanthoma
- Cutaneous metastases

Chronic cutaneous leishmaniasis and leishmaniasis recidivans:
- Lupus vulgaris
- Leprosy
- Sarcoidosis, lupus pernio
- Granuloma faciale
- Jessner lymphocytic infiltrate
- Lymphocytoma cutis
- Discoid lupus erythematosus
- Psoriasis
- Keloids
- Syphilitic gumma
- Sporotrichosis
- Rhinoscleroma
- Chronic venous ulcers

may be mistaken for malignancies, such as basal cell carcinoma, squamous cell carcinoma, or keratoacanthoma, partially attributable to their chronicity and frequent localization on the face.[5,59,99] CL can mimic many other conditions, for example, pyoderma gangrenosum, lupus vulgaris, lupus erythematosus, sarcoidosis, and granuloma annulare (Table 2). Chronic lupoid leishmaniasis and lupus vulgaris can be difficult to differentiate. In addition, the whole gamut of infectious cutaneous disorders may need to be considered within the differential diagnosis of CL, sometimes requiring extensive microbiologic, histopathologic, or systemic workup.[59] The morphologically different pictures of CL can be associated with many factors, such as the strain of the parasite, pathogenicity, virulence, host immunity, and geographic factors.[94,100]

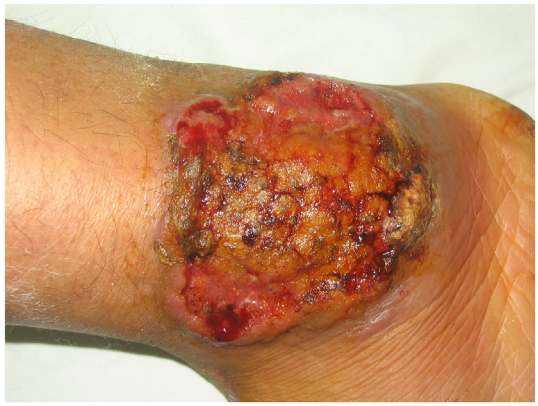

Fig. 3 Tumoral cutaneous leishmaniasis; giant ulcer on the ankle.

Tumor or squamous cell carcinoma-like leishmaniasis

Tumor or squamous cell carcinoma-like form of CL lesions appear on the face, with a predilection to affect the nose and extremities (Figure 3). When they occur on the extremities, they should be differentiated from eccrine poroma, panniculitis, lymphoma, actinomycosis or mycetoma of the foot, and amelanotic melanoma. These lesions are often observed in pregnant women and in the elderly.[96,101] The chronicity, absence of pain, and characteristic expansion of the lesions should be taken into consideration to consider a diagnosis of CL.[102–104] The ulcerative form of chronic CL most commonly occurs on the lower extremities and mainly resembles chronic venous ulcers.[96,98,102,105]

Erysipeloid leishmaniasis

The erysipeloid form of CL may be mistaken for a bacterial infection and is characterized by diffusely erythematous, infiltrated plaques over the cheeks and nose.[106] These lesions are generally not ulcerated, cover the center of the face with varying degrees of scaling, and resemble erysipelas (Figure 4). The lesions are not uniformly flat, and the initial plaque area is more indurated or elevated. Lymphadenopathy or mucous membrane involvement is absent. Erysipeloid CL may differ from erysipelas by some clinical features such as chronicity, lack of pain, and being colder with palpation than would expected be for erysipelas.[96,106–112] Erysipeloid-type CL predominantly affects middle-aged or elderly females. Skin aging and fragility in elderly patients may facilitate spread of the parasites in the case of erysipeloid CL. Posttraumatic cutaneous lesions or prolonged exposure to the sun may contribute to the occurrence of this type of disease.[56,109,113]

Similarly, CL may simulate ecthyma, a furuncle, or a carbuncle.[52] Occasionally, acute CL lesions can be secondarily infected and mimic impetigo. An infected lesion is

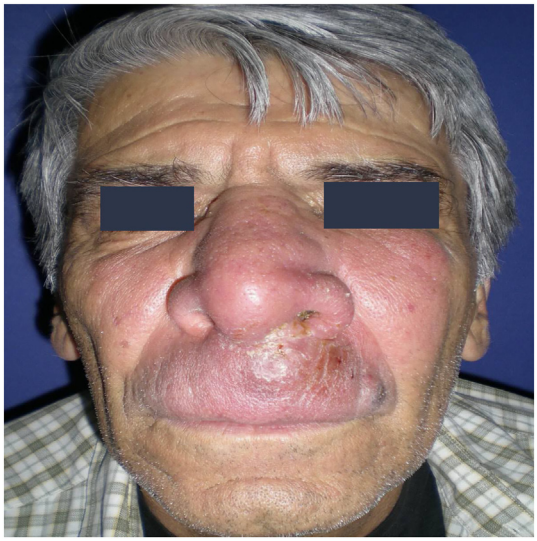

Fig. 4 Erysipeloid cutaneous leishmaniasis; infiltrated, ill-defined, erythematous plaque on the face.

erythematous, inflamed, warm to palpation, painful, and crusted. Such lesions can evolve into an ulcerative form. Simultaneously, impetigo contagiosa can develop in the same area (Figure 5).[113]

Eczematous or psoriasiform leishmaniasis

Eczema-like, psoriasiform clinical variants of CL have been reported, necessitating a high index of suspicion for diagnosis.[58,102] CL may appear as erythematous scaly lesions or hyperkeratotic plaques, mimicking psoriasis (Figure 6A, B, C). Patients with HIV tend to develop more psoriasiform CL lesions. An erythematous infiltrated lesion covered by scaling and crust usually forms at a single focus and spreads peripherally.[95,113–116] Clinically, CL can manifest as acute dermatitis with vesicular lesions, oozing, crust formation or rarely, chronic eczematous lesions (Figure 7). Patients with eczematoid CL lesions may complain of pruritus.

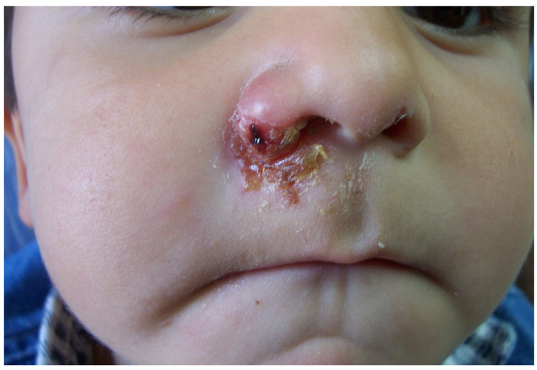

Fig. 5 Impetigo-like cutaneous leishmaniasis with yellow crust and oozing around the right nostril.

Eczematous CL lesions are localized on the extremities as nummular eczema-like or on the dorsum of hands and feet as hand eczemalike lesions. This atypical clinical presentation is mainly thought to be caused by a severe imbalance in cell-mediated immunity and is seen in patients with HIV. Histopathology shows correlation to the cutaneous findings, demonstrating acanthosis and spongiosis.[97,117–121]

Discoid lupus erythematosuslike CL

Rarely, CL mimic discoid lupus erythematosus lesions and shows the butterfly distribution on the face. It can be misdiagnosed as discoid lupus erythematosus. Atrophic plaques, central scale and peripheral papules that are seen in LR can be misleading (Figure 8). Leishmanial granulomatous dermatitis is observed in the biopsy specimen instead of interface dermatitis.[88,96]

Acneiform CL

Acnelike lesions are rarely observed in patients with CL. They appear as multiple, symmetric, reddish-brown, monomorphic acneiform papules and nodules on the face (Figure 9). The disseminated form of CL may be misdiagnosed as an acneiform eruption. This clinical condition may be misdiagnosed as granulomatous rosacea or other granulomatous dermatitis.[61,122]

Sporotrichoid CL

Importantly, the sporotrichoid form of CL should be differentiated from other cutaneous infections with a sporotrichoid pattern, for example, sporotrichosis, atypical mycobacterial infections, nocardiosis, and cat scratch disease, to name a few.[123] Sporotrichoid CL is caused by the dissemination of amastigotes to the subcutaneous tissues via the lymphatic system.[113,124] Sporotrichoid patterns of New World CL from Brazil, most of which are due to *Leishmania braziliensis,* manifest with lesions on the upper limbs, predominately in women of older ages.[124] Sporotrichoid CL is also significantly more common in Sudan and Tunisia, where it is caused by *Leishmania major*.[125,126]

In sporotrichoid CL, multiple nodular lesions extend from the main lesion in a linear pattern along lymphatic vessels over the extremities (Figure 10). The nodules, 5 to 15 mm in diameter, are soft, mobile, and nontender. They do not tend to ulcerate; if they do ulcerate, only a few do so at a later time. The amastigotes are seen in the primary but not the secondary lesions. Sporotrichoid nodules may represent host immune reactions to the lymphatic extension of *Leishmania* antigens.

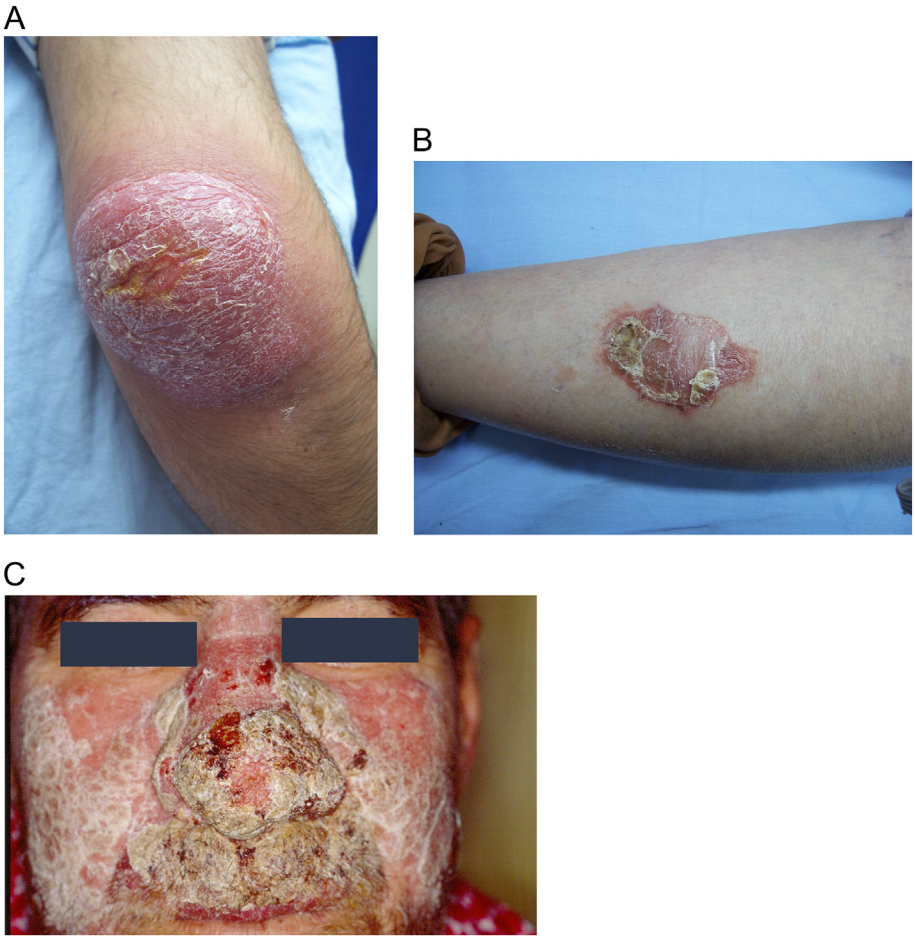

Fig. 6 Psoriasiform cutaneous leishmaniasis; erythematous and scaly plaque on the (A) elbow; (B) forearm; and (C) face in different patients.

Regional lymphadenopathy is usually not seen. Sporotrichoid CL is not associated with a poor prognosis.[88,90,96,102,127]

When topical corticosteroids or immunosuppressive drugs are used to treat CL, the lesions progressively lose nodularity and begin to flatten (Figure 11). If the lesion shows a non-healing atypical clinical picture, it signals chronic CL. Histopathologic examination will reveal granulomatous inflammation in the dermis.[122]

Anecdotal reports of CL mimicking pyogenic granuloma, otitis externa, granulomatous cheilitis, leonine facies, and dermatomyositis have been published, further expanding the clinical spectrum.[128–132] Due to its highly polymorphous

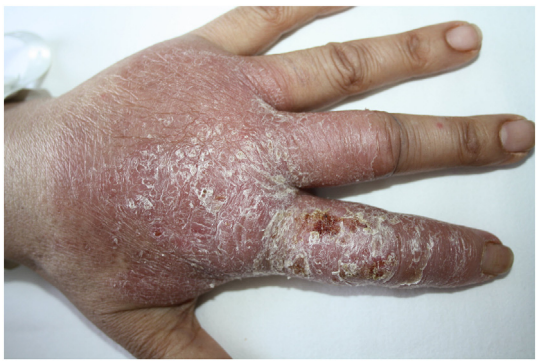

Fig. 7 Eczematous leishmaniasis; erythematous, edematous, and crusted plaque on the dorsum of the left hand, extending to the dorsa of the left index and middle fingers.

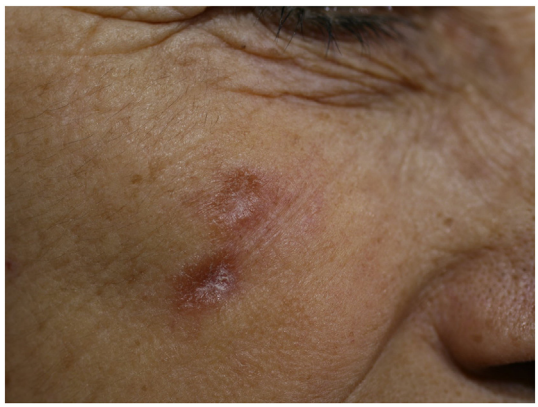

Fig. 8 Discoid lupus erythematosuslike cutaneous leishmaniasis.

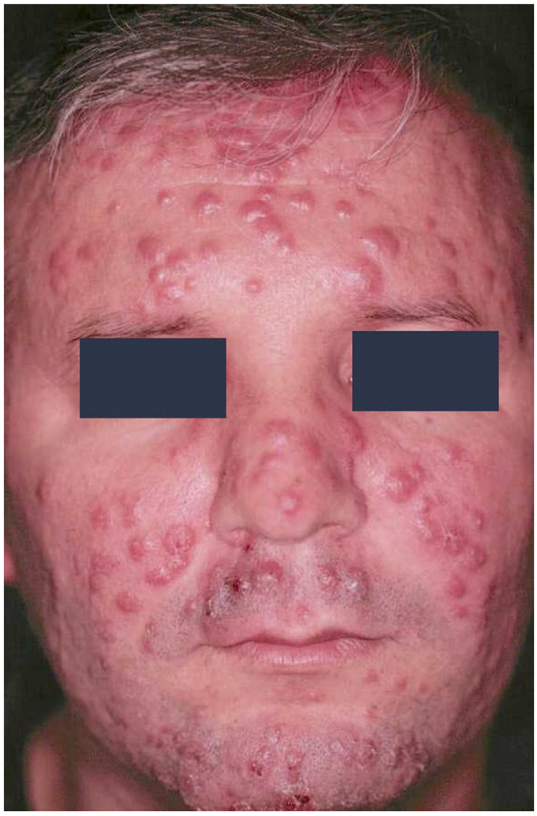

Fig. 9 Acneiform cutaneous leishmaniasis; multiple nonulcerated papulonodular lesions on the face.

nature, PDKL may simulate many other cutaneous afflictions, for example, miliaria rubra, scabies, leprosy, pityriasis versicolor, discoid lupus erythematosus, or vitiligo.[4,70,73]

The histologic differential diagnosis of CL includes other granulomatous dermatoses such as leprosy, sarcoidosis, lupus vulgaris, and granulomatous rosacea.[57,59,82,84,85] The clinical differentiation of LR from lupus vulgaris and tuberculoid leprosy can be almost impossible. In addition, other infectious pathologies characterized by parasitized macrophages, for example, rhinoscleroma, granuloma inguinale, or histoplasmosis, should be considered within the differential diagnosis of CL.[46,123] Longstanding lesions of CL may demonstrate a large number of perivascular plasma cells, resembling secondary or tertiary syphilis.[83] In challenging cases, PCR for *Leishmania*-specific DNA performed on paraffin-embedded tissue has proven to be a reliable tool for making the diagnosis with high specificity.[5,85]

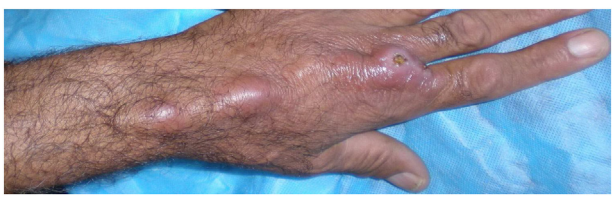

Fig. 10 Multiple sporotrichoid cutaneous leishmaniasis lesions on the extensor surface of the left upper extremity.

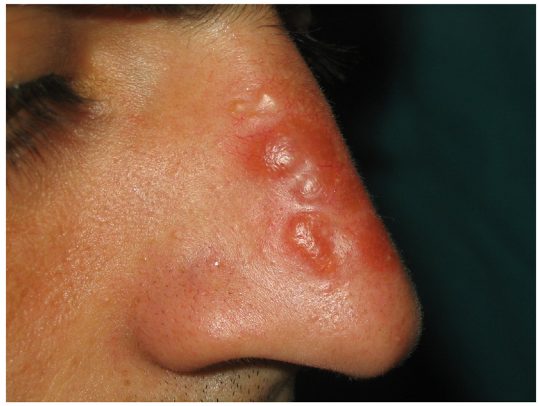

Fig. 11 Corticosteroid-modified cutaneous leishmaniasis; the lesion was treated with superpotent corticosteroid cream for 3 months.

Conclusions

The dermatologist plays a pivotal role toward the ultimate goal of eradication not only by recognizing and treating the clinical findings of the disease itself, but also by addressing the deep-rooted social implications (eg, collectively contributing to public health prevention measures and striving to eliminate social stigmatization). The World Health Organization has established multiple priority areas for research to combat leishmaniasis, emphasizing diagnostic techniques, new drug and vaccine development, and vector control[133]; however, despite collaborative and concerted efforts toward increased global awareness and disease control, leishmaniasis, unfortunately, remains a challenging and neglected infection. The great imitator, CL, creates some diagnostic difficulties for clinicians and pathologists. To diagnose an atypical lesion of CL, the region in which the patient lives, the patient's medical history, and the natural course of the lesion must be taken into consideration. If CL is considered, it should be diagnosed and treated with the most appropriate diagnostic method to reduce the progression of the disease and to control the spread of infection.

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